RESEARCH ARTICLE

Diagnosis and Outcomes of Late-Onset Wilson's Disease: A National Registry-Based Study

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ABSTRACT: Background: Wilson's disease (WD) is usually diagnosed in children and young adults; limited data exist on late-onset forms.

Objective: The aim was to characterize the clinical and paraclinical presentations, therapeutic management, and outcomes in patients with late-onset WD.

Methods: Patients diagnosed with WD after age 40 years were identified from the French Wilson's Disease Registry (FWDR). Clinical, laboratory, and imaging findings and treatment were reported at diagnosis and last follow-up.

Results: Forty-five patients were identified (median age: 49, range: 40–64) and placed in three groups according to their clinical presentation: neurological (n = 20, median diagnostic delay: 20 months), hepatic (n = 13, diagnostic delay: 12 months), and family screening (n = 12), all confirmed genetically. Six neurological patients had an atypical presentation (1 torticollis, 2 writer's cramps, 2 functional movement disorders, and 1 isolated dysarthria), without T2/fluid-attenuated inversion recovery brain magnetic resonance imaging (MRI) hyperintensities; 5 of 6 had no Kayser–Fleischer ring (KFR); 5 of 6 had liver involvement. In the neurological group, 84% of patients improved clinically, and 1 developed copper deficiency. In the hepatic group, 77% had cirrhosis; 6 patients required liver transplantation. In the screened group, 43% had mild liver involvement; 3 were not treated and remained stable; 24-h urinary copper excretion was normal in 33% of patients at diagnosis.

Conclusions: In the FWDR, late-onset forms of WD affect 8% of patients, mostly with neurological presentations. Thirty percent of the neurological forms were atypical (isolated long-lasting symptoms, inconspicuous brain MRI, no KFR). With personalized treatment, prognosis was good. This study emphasized that WD should be suspected at any age and even in cases of atypical presentation.

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Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism, with progressive copper overload in many organs, primarily the brain and liver.[1] The diagnosis of WD involves a combination of clinical, biochemical, and genetic tests.[2] WD typically presents in children, adolescents, and young adults. The mean age at diagnosis ranged from 18.5 ± 11[3] to 28 ± 9 years[4] in different registry-based studies, with a later diagnosis in neurological forms.[5]

Late-onset WD forms diagnosed after age 40 years, or even after 70 years, are rarely reported; therefore, little is known about this phenotype.[6,7] To date, a few case reports[7-14] and a European study (n = 46), with limited data on neurological phenotyping, have described patients with late-onset WD.[15] In this current study, we analyzed a cohort of patients diagnosed after age 40 years, who were identified from the French Wilson's Disease Registry (FWDR). Our aim was to characterize their clinical and paraclinical presentations, as well as their therapeutic management and outcomes.

Patients and Methods

This study was carried out by the National Reference Centre for Wilson's Disease (NRCWD) in Paris, working in collaboration with the French WD network. All patients had given their informed consent for genetic analysis and anonymous study of their data before their inclusion in the FWDR. The present study was approved by the Institutional Review Board (IRB00003888, IORG0003254, FWA00005831) for the French Institute for Medical Research and Health (INSERM) (no.: 19-550).

Study Design

Patients diagnosed with WD after age 40 years between June 1974 and 2016 were selected from the FWDR for this longitudinal cohort study. Patients had confirmed WD with a Leipzig score ≥4.[16] They were classified into three groups according to their diagnostic mode: (1) neurological (hepatic features could be associated); (2) hepatic (elevated liver enzymes, hepatomegaly/steatosis at liver ultrasound, compensated cirrhosis, and decompensated cirrhosis with or without encephalopathy); and (3) diagnosed by family screening or incidentally.

At Diagnosis

Sex; past medical history; age at first symptoms and at diagnosis; initial phenotype; clinical examination; and laboratory, ophthalmological, genetic, and imaging findings were reported. Neurological signs (tremor, writing difficulties, gait disorder, dysarthria, drooling, dystonia, cerebellar syndrome, parkinsonism, and cognitive impairment) and psychiatric disorders (depression, anxiety, psychosis, or behavioral disorders) were recorded. Slit lamp examination searched for the presence of Kayser–Fleischer ring (KFR).[17] Hepatic assessment included laboratory tests (blood count, liver enzymes, and prothrombin time), presence of hepatic copper if available, liver ultrasonography, and/or transient-elastography-Fibroscan to determine the hepatic score from 0 to 6 (progressive grading ranging from no liver abnormalities to decompensated cirrhosis).[18] When liver transplantation was performed, the hepatic score was rated as 0 during follow-up. Copper tests included serum total copper, serum ceruloplasmin (immunonephelometric method), and 24-h urinary copper excretion (UCE). Non-ceruloplasmin-bound copper (NCC) was calculated as follows: NCC (μmol/L) = serum copper (μmol/L) − 0.047 × ceruloplasmin (mg/L).[19,20] For patients diagnosed after 2010, the direct assay of NCC (exchangeable copper) and calculation of the relative exchangeable copper (REC)[18,21-23] were recorded. The REC is considered a valuable biomarker for WD diagnosis, whatever its clinical form,[18,21-23] and is defined as the ratio of the direct assay of exchangeable copper to total serum copper.

Diagnosis was confirmed using molecular analysis of the *ATP7B* gene.

Brain images were obtained using a 1.5-T brain magnetic resonance imaging (MRI) with fluid-attenuated inversion recovery (FLAIR), T2, T1, and T2* sequences. All brain MRIs were reviewed by two experts from the NRCWD (A.P. and C.N.), who assessed T2/FLAIR hyperintensities.[18] In neurological patients, MRIs were also scored using the method of Dusek et al.[24]

All treatments (D-penicillamine, trientine 2HCl, zinc salts, and liver transplantation) and their tolerance were reviewed.

At the Most Recent Follow-Up

Duration of follow-up, age, phenotype, clinical features, presence of KFR, brain MRI score, hepatic score, serum and urinary copper levels, and treatment were documented. Incidence and causes of death were recorded.

Statistical Analysis

The data are presented as median values with interquartile ranges (IQR) for continuous variables and

numbers (percentages) for qualitative variables. All analyses were performed using statistical programming language R, version 4.0.3 (R Project for Statistical Computing). A nonparametric Wilcoxon test was performed to compare two distributions, whereas a nonparametric Kruskal–Wallis test was performed to compare three distributions. A χ^2 test or Fisher's test was used to test the relationships between categorical variables, based on the conditions of test validity. Box plots were used to represent copper findings at diagnosis and at follow-up by clinical presentation. All tests were bilateral and performed using a 2-tailed level of significance set at $P < 0.05$.

Results

A total of 552 patients with WD were included in the FWDR. Forty-five (8%) were at least aged 40 years at diagnosis (24 were aged 40–50 years, and 21 were ≥50 years). There were 20 men (44%). The median age at symptom onset was 45 years (IQR: 42–50) and at diagnosis 49 years (IQR: 43–53). The oldest patient was aged 64 years at diagnosis.

Twenty patients (44%) had a neurological presentation, 13 (29%) had a hepatic presentation, and 12 (27%) were diagnosed by family screening or incidentally (Table 1). Age at first symptoms, age at diagnosis, and time to diagnosis were not significantly different between the neurological and hepatic groups. Some previous manifestations were suggestive of WD: depression (n = 4), bipolar disorder (n = 1), anorexia nervosa (n = 2), unexplained transient hepatitis or chronic liver disease (n = 3), and cytopenia (n = 1).

Figure 1 shows copper findings between baseline and the most recent follow-up. At baseline, the 24-h UCE values were normal in 7 of 21 patients (33%), including 4 from the screened group. The 24-h UCE values differed significantly between the groups ($P = 0.04$), with higher levels among hepatic patients.

The sensitivity of REC for WD diagnosis was 82% in symptomatic patients and 86% in screened patients. The test failed to diagnose WD in 3 patients with hepatic form (all had cirrhosis, high UCE, and low ceruloplasmin), in 1 patient with atypical neurological presentation and in 2 screened patients. The REC was greater than 15% in 5 of 7 patients with a normal UCE and between 8% and 15% for the remaining 2 of 7 patients.

Full genetic data were available for 39 of 45 patients (87%). Two mutations of the *ATP7B* gene were found in all patients except 1 patient (one mutation found) who had a classic neurological form. Most patients carried heterozygous mutations (28 of 39); the most frequent mutation was H1069Q.

The initial treatment and tolerance are summarized in Table 2. Most patients received D-penicillamine as first-line therapy (57%). There was no significant difference in treatment tolerance. Eighteen patients (41%) needed a second-line therapy, mainly due to lack of efficacy.

Table 3 presents patients' characteristics at the most recent follow-up, 6.5 years (median) after diagnosis. Seven patients were lost to follow-up, and 2 died.

Neurological Group (n = 20)

At diagnosis (Tables 1 and 4).

Neurological patients presented with writing difficulties (15 of 20, writer's cramp, micrographia), dysarthria (12 of 20), dystonia (10 of 20), tremor (10 of 20), gait impairment (9 of 20), cognitive impairment (8 of 20), parkinsonism (7 of 20), hypersalivation (4 of 20), and cerebellar syndrome (3 of 20). Psychiatric symptoms included depression (4 of 20) and behavioral disorders (2 of 20, disinhibition, apathy).

Fourteen neurological patients (70%) presented typical signs of WD, either isolated or associated, and had a median diagnostic delay of 19 months (IQR: 11.5–33). In all 10 patients whose brain MRIs were available, imaging was abnormal with FLAIR hyperintensities in the basal ganglia, thalamus, mesencephalon, and pons. KFR was present in all these classic neurological patients. The median hepatic score was 1/6, including only 1 patient with cirrhosis. Three patients had thrombopenia.

Six patients from the neurological group (30%) presented with isolated long-lasting symptoms of WD (Table 4), with a median delay of 120 months before diagnosis (IQR: 12–120). One patient, aged 47 years, presented with isolated torticollis for 10 years, treated at some point with botulinum toxin. He subsequently developed writer's cramp, dysarthria, cerebellar ataxia, and mild tremor of the right hand, which enabled the diagnosis of WD. Two brothers were in this group: one had isolated writer's cramp for a year before being diagnosed with WD at age 61 years, when he was also presenting with cirrhosis; the other one (aged 58 years) had writer's cramp with hand tremor for 10 years before being diagnosed. Two patients presented with functional movement disorders (FMD), based on Gupta and Lang diagnostic criteria (eg, inconsistency in movements over time, incongruence with typical features of movement disorders, and suggestibility)[25]: one had paroxysmal myoclonus of the limbs and the head, with normal neurological examination between the episodes of abnormal movement, whereas the other had an inconsistent and variable tremor of both hands and head, associated with balance difficulties. Electrophysiological analysis of both patients provided further support for FMD diagnosis. The first one displayed muscular jerks of long duration whose diffusion did not follow either the cortico-spinal or the proprio-spinal descending pathway, with variability in the contraction interval of the different muscles and of their activation sequence. The analysis of the second patient found no

TABLE 1 *Demographic, clinical, and paraclinical data of patients with late-onset Wilson's disease at diagnosis*

Variable	Neurological group (n = 20)	Hepatic group (n = 13)	Screened group (n = 12)	All (n = 45)	*P*-value
Males	10 (50)	5 (38)	5 (42)	20 (44)	0.79
Females with history of pregnancy	5/6 (83)	5/5 (100)	5/6 (83)	15/17 (88)	0.43
Age at first symptoms (y), median (IQR)	44 (41–49)	45 (42–51)	NA	45 (42–50)	0.24
Age at diagnosis (y), median (IQR)	46 (43–52)	51 (44–55)	48 (43–51)	49 (43–53)	0.55
Time from onset of first symptoms to diagnosis, months, median (IQR)	20 (12–66)	12 (1–24)	NA	19 (8–60)	0.36
Neurological involvement					
Neurologic symptoms or signs	19/19 (100)	3/12 (25)[a]	0/9	22/39 (56)	<0.005
Psychiatric symptoms	6/19 (32)	2/11 (18)	1/9 (11)	9/39 (23)[b]	>0.99
Abnormal brain MRI with T2/FLAIR hyperintensities	10/16 (63)	3/8 (38)	0/3	13/27 (48)	0.13
Details of the T2/FLAIR hyperintensities					0.13
0 (no lesion)	6/16 (38)	5/8 (63)	3/3 (100)	14/27 (52)	
1–2 locations	5/16 (31)	1/8 (13)	0/3	6/27 (22)	
3–4 locations	5/16 (31)	2/8 (25)	0/3	7/27 (26)	
5–6 locations	0/16	0/8	0/3	0/27	
Pallidum hypointensity	5/16 (31)	1/8 (13)	0/4	6/28 (21)	0.54
Ophthalmologic involvement					
Presence of KFR	14/19 (74)	6/10 (60)	2/10 (20)	22/39 (56)	0.026
Hepatic involvement					
Liver involvement (hepatic score ≥ 1)	12/16 (75)	13/13 (100)	3/7 (43)	28/36 (78)	0.026
Hepatic score					
0–1 (normal hepatic function, HMG)	13/16 (81)	2/13 (15)	8/8 (100)	22/36 (61)	0.001
2 (chronic hepatitis)	1/16 (6)	1/13 (8)	0/8	2/36 (6)	
3–4 (acute hepatitis)	0/16	0/13	0/8	0/36	
5–6 (cirrhosis)[c]	2/16 (13)	10/13 (77)	0/8	12/36 (33)	
Liver enzymes, median (IQR)					
n	15	9	6	30	
AST, U/L	25 (23–32)	52 (37–114)	34 (33–38)	34 (25–44)	0.009
ALT, U/L	26 (21–32)	81 (35–118)	58 (43–76)	37 (25–73)	0.017
Platelets, G/L, median (IQR)	181 (156–238)	108 (90–164)	257 (206–301)	181 (140–255)	0.015
Fibroscan (kPa), median (IQR)[d]	4.8 (4.5–10.3)	30.6 (19.2–41.9)	6.7	6.7 (4.6–12.1)	0.33

Note: Values are numbers of patients (%) or numbers of patients/those with available data (%), unless specified otherwise.
Abbreviations: IQR, interquartile ranges; NA, not applicable; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; KFR, Kayser–Fleischer ring; HMG, hepatomegaly; AST, aspartate aminotransferase; ALT, alanine aminotransferase; U/L, units per liter; G/L, giga per liter.
[a]Hepatic encephalopathy.
[b]Psychiatric symptoms included depression (n = 7) and behavioral disorder (n = 2, neurological patients).
[c]Three patients with decompensated cirrhosis had available MELD scores (32, 18 and 29).
[d]Data were available in 2 hepatic patients, 6 neurological patients, and 1 screened patient.

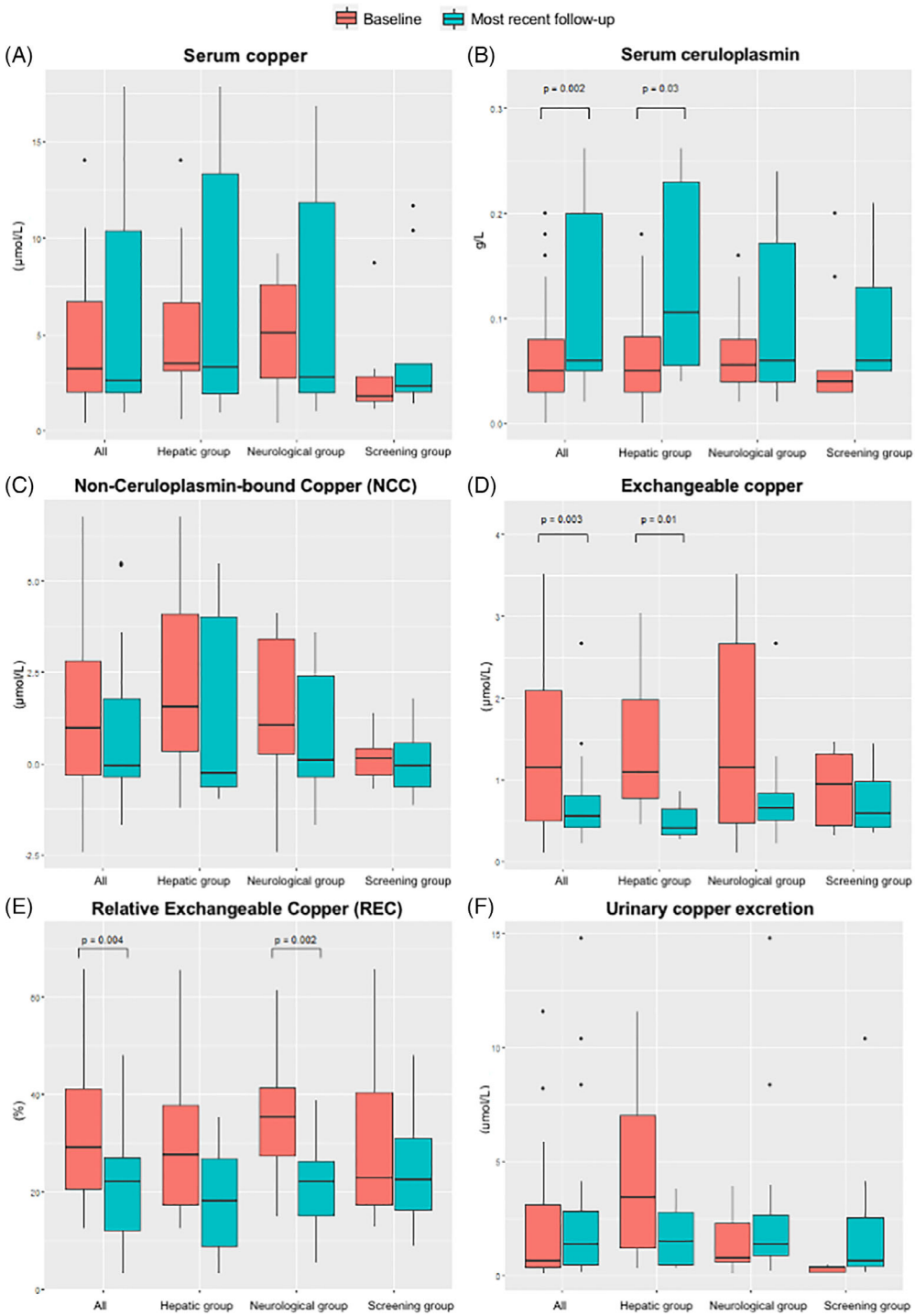

FIG. 1. Serum and urine copper findings between baseline (red) and the most recent follow-up (blue) in patients with available data: all patients, patients from the hepatic group, patients from the neurological group, and patients diagnosed by screening represented by box plots. (**A**) Serum copper (normal range: 13–22 µmol/L); (**B**) serum ceruloplasmin (normal range: >0.2 g/L). Ceruloplasmin levels increased significantly ($P = 0.031$) at the most recent follow-up in hepatic patients. (**C**) Calculated non-ceruloplasmin-bound copper (NCC) (normal range: <1.6 µmol/L); (**D**) exchangeable copper (normal range: <1.5 µmol/L). The exchangeable copper decreased significantly at the most recent follow-up in hepatic patients ($P = 0.011$). (**E**) Relative exchangeable copper (REC) (normal range: <8%). Seven of 10 hepatic patients had an REC >18.5%; 12 of 13 neurological patients had an REC >18.5%; 5 of 7 patients diagnosed by screening had an REC >15%. (**F**) Urinary copper excretion (UCE) (normal range: 0.02–0.40 µmol/L). The 24-h UCE values were significantly higher at diagnosis in hepatic patients ($P = 0.04$) compared to patients diagnosed by screening and neurological patients. There were no other significant differences in copper findings between the groups. [Color figure can be viewed at wileyonlinelibrary.com]

tremor or other abnormal movement. The sixth patient had isolated dysarthria for almost 10 years, with progressive worsening over time, and then developed tremor of upper limbs and walking problems.

TABLE 2 *First- and second-line treatments and tolerance*

Variable	Neurological group	Hepatic group	Screened group	All
First-line treatment				
n	19	13	12	44
D-Penicillamine	12 (63)	8 (62)	5 (42)	25 (57)
Zinc acetate	5 (26)	1 (8)	2 (17)	8 (18)
Trientine salt	2 (11)	0	2 (17)	4 (9)
Liver transplantation	0	4 (31)	0	4 (9)
No treatment	0	0	3 (25)	3 (7)
Clinical worsening under treatment	7/18 (39)	2/12 (17)[a]	1/8 (13)	10/38 (26)
Presence of D-penicillamine side effects leading to discontinuation of treatment[b]	3/18 (17)	2/12 (17)	0/8	5/38 (13)
Second-line treatment				
n	11	5	2	18/44 (41)
D-Penicillamine	0	0	1 (50)	1 (6)
Zinc acetate	4 (36)	1 (20)	1 (50)	6 (33)
Trientine salt	3 (27)	2 (40)	0	5 (28)
Copper chelator + zinc acetate	2 (18)	0	0	2 (11)
Liver transplantation	1 (9)	2 (40)	0	3 (17)
No treatment	1 (9)	0	0	1 (6)

Values are numbers of patients (%) or numbers of patients/those with available data (%).
[a]After 1 month of treatment: fulminant hepatitis (n = 1), decompensation of cirrhosis (n = 1).
[b]Side effects: asthenia, weight loss, arthralgia, and proteinuria.

Surprisingly brain MRI of all 6 patients showed no T2/FLAIR hyperintensities (Fig. S1); however, the brain MRI severity scale, according to the recent validated score by Dusek et al, revealed mild atrophy in 4 of them[24] (Table S1). Only 1 of these 6 patients had a KFR. Five of 6 patients had liver involvement, including 1 with cirrhosis. Serum copper was low, and REC was elevated in all patients. Urinary copper was elevated in 4 of 6 patients. The 2 patients with normal UCE had high intrahepatic copper. All these atypical neurological forms of late-onset WD were confirmed by molecular analysis (Table S2). Three mutations were novel: their pathogenicity was assessed using the American College of Medical Genetics and Genomics classification,[26] based on general population databases, missense variant prediction algorithms/software, international databases of pathogenic variants, and the literature.

After 5.0 Years (IQR: 3.0–12.8) of Follow-Up.

Follow-up was available for 19 patients with neurological presentation (Table 3). All patients were treated, including 12 of 19 with D-penicillamine (Table 2). Sixteen patients improved clinically, including 7 who recovered completely. Persistent symptoms included dysarthria (8 of 19), tremor (7 of 19), writing difficulties (6 of 19), dystonia (6 of 19), gait disorder (5 of 19), parkinsonism (3 of 19), depression (3 of 19), cognitive impairment (2 of 19), behavioral disorder (2 of 19), cerebellar syndrome (2 of 19), hypersalivation (1 of 19), and anxiety (1 of 19). The REC values decreased significantly in the neurological patients at the most recent follow-up ($P = 0.002$), unlike hepatic and screened patients (Fig. 1).

Five of the 6 patients with atypical neurological presentations were clinically stable or improved (Table 4). Of these 6 patients, brain MRI remained normal in 3 of them, worsened slightly in 1, and was not repeated in 2.

Overall, 3 patients with neurological forms worsened despite treatment. Two patients from the classic presentation group were treated using chelators and had a progressive worsening of their parkinsonism and dysarthria after initiation of chelation. The third one belonged to the atypical group and developed copper deficiency 20 years after initiation of treatment, resulting in severe chronic sensorimotor polyneuropathy of the lower limbs (Table 4, patient 3). At that time, his hepatic score was stable (1/6), UCE and exchangeable copper levels were low, and brain and medullar MRI findings remained normal. Other causes of polyneuropathy were ruled out. After zinc acetate was withdrawn, the patient slowly improved, although after 8 years he still experienced deep and superficial sensory disturbances, writer's cramp, and

TABLE 3 *Characteristics of patients with late-onset Wilson's disease at the most recent follow-up*

Variable	Neurological group	Hepatic group	Screened group	All	*P*-value
n	18	11	9	38	
Time from diagnosis to the most recent follow-up (y), median (IQR)	5.0 (3.0–12.8)	4.0 (3.5–9)	7.0 (7.0–22.0)	6.5 (3.0–13.0)	0.32
Age at last follow-up (y), median (IQR)	57 (48–64)	60 (52–63)	56 (52–62)	58 (52–64)	0.86
Brain MRI involvement					
n	15	4	1	20	
Time from first MRI to the most recent one (y), median (IQR)	3.0 (2.0–11.0)	3.0 (1.8–4.1)	2.0 (2.0–2.0)	3.0 (2.0–6.8)	0.43
Evolution of T2/FLAIR hyperintensities					
Improvement	4/13 (31)	2/3 (67)	NA	6/16 (38)	0.42
Stability	6/13 (46)	0/3	NA	6/16 (38)	
Worsening	3/13 (23)	1/3 (33)	NA	4/16 (25)	
Ophthalmologic involvement					
n	11	6	1	18	
Time from first slit lamp examination to the last one (y), median (IQR)	3.0 (2.0–8.8)	3.0 (2.0–3.5)	25.0 (25.0–25.0)	3.0 (2.0–7.5)	0.21
Total or partial disappearance of KFR	9 (82)	3 (50)	1 (100)	13 (72)	0.48
Hepatic involvement					
Evolution of the hepatic score					
Improvement[a]	3/15 (20)	7/10 (70)	2/8 (25)	12/33 (36)	0.019
Stability	11/15 (73)	3/10 (30)	3/8 (38)	17/33 (52)	
Worsening	1/15 (7)[b]	0	3/8 (38)[c]	4/33 (12)	
Liver enzymes, median (IQR)					
n	17	8	9	34	
AST, U/L	29 (23–33)	28 (26–30)	24 (20–32)	28 (23–33)	0.37
ALT, U/L	30 (17–35)	31 (25–42)	33 (25–42)	31 (19–37)	0.63
Platelets, G/L, median (IQR)	215 (159–255)	213 (176–235)	224 (207–262)	216 (182–260)	0.19
Fibroscan (kPa), median (IQR)[d]	6.5 (4.6–10.6)	6 (5.7–9.2)	5.3 (4.7–5.4)	5.6 (4.8–6.8)	0.33
Hepatocellular carcinoma	0	1/11 (9)	1/10 (10)	2/37 (5)	0.29

Values are numbers of patients (%) or numbers of patients/those with available data (%), unless specified otherwise.
[a]Including patients who received liver transplantation (for whom the hepatic score was 0/6).
[b]One liver ultrasound was slightly worse despite treatment (zinc acetate).
[c]Including 1 treatment-free patient.
[d]Data were available for 4 hepatic patients, 13 neurological patients, and 7 screened patients.
Abbreviations: IQR, interquartile range; magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; NA, not applicable; KFR, Kayser–Fleischer ring; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

dysarthria. He is no longer being treated for WD but undergoes regular clinical and laboratory tests. His liver status has remained stable.

In 10 patients (9 receiving D-penicillamine and 1 zinc acetate), first-line treatment was replaced after a median of 1.5 years by another medication because of lack of efficacy (n = 5, including the one treated with zinc acetate), poor tolerance (n = 3), and undetermined reasons (n = 2) (Table 2).

Hepatic Group (n = 13)

At diagnosis (Table 1).

Among patients with hepatic late-onset WD, 3 (23%) presented with elevated aminotransferases and 10 (77%) with cirrhosis: compensated cirrhosis (n = 3) (esophageal varices [n = 2] and splenomegaly with thrombocytopenia [n = 1]) or decompensated cirrhosis (n = 7) (encephalopathy [n = 3] and ascites with lower-limb edema [n = 4]).

TABLE 4 *Description of 6 patients with late-onset Wilson's disease and atypical neurological presentation*

Patient, sex, age at diagnosis (y), family link	First neurological symptoms	Age at first symptoms (y)	Other neurological symptoms at diagnosis	Molecular analysis (both mutations)	Liver assessment	KFR 0 = no; 1 = yes	Brain MRI	Serum copper (µmol/L) (N 13–22)	Cp (g/L) (N > 0.2)	NCC (µmol/L) (N < 1.6)	ExCu (µmol/L) (N 0.62–1.15)	REC (%) (N < 8%)	UCE (µmol/L) (N < 0.40)	Treatment	Evolution at the most recent follow-up
1. Male, 56	Torticollis	47	Writer's cramp, dysarthria, cerebellar ataxia, mild tremor of one hand	Ile542Thr 2731-1G > A	Hepatic score: 1/6 Liver US: steatosis. Fibroscan: 4.4 kPa. Liver enzymes N PLT 212.	0	N	3.1▼	0.05▼	0.75	1.15▲	37.1▲	0.62▲	Zinc acetate 150 mg/d	After 6 y, stability of the cervical dystonia; no dysarthria. Hepatic score stable at 1/6
2. Male, 61 (patient 3's brother; one affected sister in screened group)	Writer's cramp	60	0	Phe714Leu 1544-1707del	Hepatic score: 5/6. Liver US: cirrhosis. Liver enzymes N.	0	N	1.24▼	0.05▼	−1.11	0.47▼	37.9▲	1.8▲	DP 900 mg/d (7 y), then zinc acetate 150 mg/d	After 11 y, no more writer's cramp. Stabilization of the cirrhosis.
3. Male, 58 (patient 2's brother; one affected sister in screened group)	Writer's cramp, hand tremor	48	0	Phe714Leu 1544-1707del	Hepatic score: 1/6. Liver MRI: iron overload. Liver enzymes N. PLT 181.	0	N	1.77▼	0.05▼	−0.58	0.1▼	29.4▲	1.21▲	DP 900 mg/d (3 y), trientine 900 mg/d (4 y), zinc acetate 150 mg/d (13 y)	After 28 y (20 y of treatment and 8 y without treatment), stability of writer's cramp, no more hand tremor, persistence of neuropathy due to copper deficiency. Hepatic score stable at 1/6.
4. Female, 50	Balance disorder, functional tremor (hands and head)	50	0	Met665Ile Thr1232Pro	Hepatic score: 1/6. US: steatosis, HMG. Liver enzymes N. Hepatic copper: 7.45 µmol/g (N < 0.4/WD > 4) PLT 303.	0	N	2.61▼	0.08▼	−1.15	0.39▼	14.9▲	0.06	Zinc acetate 150 mg/d	After 2 y, asymptomatic. Hepatic score stable at 1/6.
5. Female, 54 (one affected brother in screened group)	Functional myoclonus (four limbs and head)	43	0	Met645Arg Met645Arg	Hepatic score: 0/6. Liver US: N. Liver enzymes N. PLT 256. Hepatic copper: 3.97 µmol/g (N < 0.4/WD > 4)	0	N	1.39▼	0.06▼	−1.43	0.49▼	35.3▲	0.1	Zinc acetate 150 mg/d	After 4 y, no more abnormal movements. Hepatic score at 1/6.

(Continues)

TABLE 4 *Continued*

Patient, sex, age at diagnosis (y), family link	First neurological symptoms	Age at first symptoms (y)	Other neurological symptoms at diagnosis	Molecular analysis (both mutations)	Liver assessment	KFR 0 = no; 1 = yes	Brain MRI	Serum copper (µmol/L) (N 13–22)	Cp (g/L) (N > 0.2)	NCC (µmol/L) (N < 1.6)	ExCu (µmol/L) (N 0.62–1.15)	REC (%) (N < 8%)	UCE (µmol/L) (N < 0.40)	Treatment	Evolution at the most recent follow-up
6. Male, 40	Isolated dysarthria for almost 10 y	30	Tremor, gait disorder, attention disorder	His1069Gln His1069Gln	Hepatic score: 1/6. Liver US: steatosis. Liver enzymes N. PLT 150.	1	N	2.04▼	0.02▼	1.10	0.33▼	46.5▲	2.29▲	Zinc acetate 150 mg/d	After 13 y, stability of dysarthria, improvement in tremor. Hepatic score stable at 1/6.

Abbreviations: KFR, Kayser–Fleischer ring; MRI, magnetic resonance imaging; Cp, ceruloplasmin; DP, NCC, non-ceruloplasmin-bound copper; ExCu, exchangeable copper (direct dosage of the free copper); REC, relative exchangeable copper (equal to exchangeable copper/total copper); UCE, urinary copper excretion; ▼, low value; ▲, high value; D-penicillamine; PLT, platelets (G/L); HMG, hepatomegaly; WD, Wilson disease; N, normal; ND, no data; US, ultrasound.

One patient had acute liver failure. Platelets were significantly lower in hepatic patients compared to the two other presentations ($P = 0.015$), and liver enzymes were significantly higher (aspartate aminotransferase, $P = 0.009$; alanine aminotransferase, $P = 0.017$). Sixty percent of hepatic patients had a KFR, mainly cirrhotic patients. Three of the 8 patients with initial brain MRI available had hyperintensities in the basal ganglia, suggestive of neuropathological changes secondary to copper deposition. Two patients with encephalopathy displayed severe underlying neurological signs of WD, 1 of whom had a 1-year history of psychomotor impairment before the onset of hepatic decompensation. Examination by a neurologist 3 months later found axial dystonia, *risus sardonicus*, blepharospasm, and dysexecutive frontal syndrome. Neurological examination of another patient revealed signs of central pontine myelinolysis and post-intensive care neuropathy. Brain MRI findings in these 2 patients were abnormal.

After 4 Years (IQR: 3.5–9) of Follow-Up.

Hepatic score improved in 70% of patients at last follow-up (Table 3). Ultrasound abnormalities improved in all patients. One patient who was initially encephalopathic displayed persistent dysarthria, swallowing disorder, parkinsonism, walking problems, frontal syndrome, and mood disorder. KFR disappeared in 3 of 6, and brain MRI improved in 2 of 3 patients with available follow-up data.

Between baseline and the most recent follow-up, serum ceruloplasmin levels increased significantly ($P = 0.031$) and exchangeable copper decreased significantly ($P = 0.011$), in contrast to neurological patients and screened patients (Fig. 1).

Five patients required a second-line therapy after a median of 9 months (Table 2). Four patients underwent liver transplantation as first-line therapy and 2 patients as second-line therapy due to deterioration (cirrhotic decompensation and acute liver failure).

Screened Patients (n = 12)

At diagnosis (Table 1).

Eleven patients were diagnosed by family screening, and 1 was diagnosed fortuitously when being assessed for recurrent vasovagal malaise, for which copper tests were performed. She had a normal brain MRI, low serum copper and ceruloplasmin, and normal UCE at diagnosis. Three of 7 patients for whom full data were available were related to other patients with late-onset WD. When available (n = 3), brain MRI was normal. KFR was present in 2 of 10 patients. Liver assessments were abnormal in 3 of 7 patients, with minimal liver ultrasound abnormalities. Three patients with normal copper balance were not treated but followed a low-copper diet.

After 7.0 Years (IQR: 7.0–22.0) of Follow-Up.

All screened patients remained free of neurological symptoms (Table 3). The median hepatic score was 1/6 (IQR: 0–1). One patient with isolated hepatomegaly at

diagnosis was treated with D-penicillamine and developed cirrhosis. He had hepatocellular carcinoma 14 years after diagnosis. The 3 untreated patients remained asymptomatic with normal neurologic examination after 7, 2, and 7 years; one developed hepatomegaly with moderately increased hepatic copper (3.6 μmol/g, N < 3.3), and another had a subnormal UCE (0.40 μmol/L, N < 0.40).

Discussion

In this national registry-based study, 8% of patients with WD had a late-onset form diagnosed after age 40 years. This is twice as much as that reported in the 2007 European study.[15] This discrepancy may be due to improved family screening and the discovery of new mutations. The median age at diagnosis was 49 years, in line with the data of the European study.[15] Most of the patients presented with neurological symptoms. Those with a hepatic presentation displayed severe forms: a great majority had cirrhosis, and 46% of them required liver transplantation.

The most intriguing result of our study was that 30% of the patients with late-onset neurological WD presented with atypical neurological symptoms such as long-standing isolated dysarthria, focal dystonia (cervical dystonia or writer's cramp), or FMD (functional tremor/myoclonus confirmed by electrophysiological analysis). In the literature, one case report describes a 25-year-old man with WD presenting with paroxysmal dystonia over several years.[27] The association between functional symptoms and neurological disorders is increasingly reported. A recent large multicenter study of 410 patients with functional motor disorders showed that 22% had comorbid neurological diseases.[28] In these patients, functional symptoms could appear before the diagnosis of the neurological condition.[28] In Parkinson's disease, associated functional neurological disorders are not rare[29] and are typically expressed on the side most affected by parkinsonism.[30] The association between functional and "organic" disorders may be due to common neurophysiological abnormalities.[30-32] In late-onset WD, these presentations are very misleading, especially because none of the 6 patients with atypical neurological form had brain MRI hyperintensities suggestive of WD (however, atrophy was present in 4 of them). Moreover, most of them had no KFR. In contrast, in classic early-onset WD cohorts, more than 90% patients with neurological forms have abnormal brain MRI.[24,33] The UCE and REC were helpful to guide the diagnosis toward WD before genetic confirmation. These peculiar late-onset neurological presentations have not previously been described to our knowledge. They appear different from purely psychiatric presentations of WD in which brain imaging findings can be normal. It is difficult to know if neurological symptoms were due to copper toxicity in these patients. Copper was not available in the cerebrospinal fluid. However, it has been shown in an anatomopathological study that copper can be increased in the brain even in pure hepatic forms without neurological symptoms or brain imaging abnormalities.[34] Thus far, neither the existence of modifier genes nor specific mutations of the ATP7B gene are known to be linked to such atypical neurological phenotypes.[35] Interestingly, one of the responsible mutations for WD in an atypical case (homozygous Met645Arg variant) has recently been shown to cause exon skipping, resulting in 30% wild-type expression,[36] and may explain the late presentation. One may wonder whether some of the mutations lead to slower copper deposition in the brain and cornea. Longitudinal follow-up of these patients will help us to specify these peculiar presentations. These data should encourage neurologists to consider a diagnosis of WD more often in patients after age 40 years. A history of psychiatric disorders (depression, bipolar disorder, and anorexia nervosa) and laboratory abnormalities (isolated thrombocytopenia and elevated liver enzymes) were suggestive of WD in a few patients and should be considered as red flags.[37]

The diagnosis of late-onset neurological WD seems therefore challenging. In our study, the median diagnostic delay of neurological patients was longer (20 months; range: 0–180) than that in the classic early-onset forms[3-5] (13.9 months among patients in the FWDR[3]). In the European late-onset cohort,[15] patients with neuropsychiatric WD had a median diagnostic delay of 2.8 years (range: 0–15). The specific organization of the WD network in France, with dedicated WD centers throughout the country, may explain these differences between the European and French cohorts.

Seventy percent of neurological patients developed typical signs of neurological WD (dystonia, tremor, dysarthria, and drooling) associated with abnormal brain MRI findings and KFR and liver disease in 75%. Cirrhosis was infrequent (13%) but may have been underestimated as liver biopsy was not performed. This data should encourage neurologists to look systematically for liver involvement (liver biology and liver ultrasound at least) in neurological WD patients. The diagnostic features and the evolution of neurological patients were similar to those described in the classic early-onset forms.[5]

In hepatic patients, a high rate of cirrhosis (77%) was reported at diagnosis, including 3 cases of fulminant decompensation with encephalopathy. The severity of liver damage at diagnosis should encourage physicians to screen widely for WD in the event of liver disease of unknown etiology, regardless of age, even in the case of severe presentation (eg, decompensated cirrhosis and acute liver failure).[10] This is worthwhile because treatment is highly effective and hepatocellular carcinomas are not rare. In the hepatic group, the median value of REC was 27.6%, and KFR was present in more than 50% of patients, which did not differ from classic forms.[38] Our findings were similar to that of Ferenci *et al* in late-onset forms.[15]

Brain MRIs were not always routinely performed in hepatic patients. Some of them had minimal neurological signs at diagnosis, which were not identified until later. Similarly, screened patients did not have a systematical screening for KFR or brain abnormalities. This highlights the need for multidisciplinary management of WD, particularly at diagnosis and in atypical forms.

When WD is suspected, laboratory tests are systematic. The previous European study in patients with late-onset WD[15] reported that the diagnostic criteria and genetic tests were the same as those for classic forms. In our study, UCE levels were significantly higher in hepatic patients than in the other groups, which has been previously described.[39] However, the UCE value could be normal, unlike ceruloplasmin and serum copper levels which were always low, increasing the difficulty in diagnosing atypical neurological forms. The REC is already known to have high sensitivity and specificity in diagnosing classic forms.[21-23] In this late-onset WD study, REC was less powerful than in the classic forms; results should be confirmed in a larger cohort.

As laboratory findings may be misleading, a confirmation of late-onset WD could come only from molecular analysis of the *ATP7B* gene. Two mutations were reported in all patients with available data, except 1 who had only one mutation. False negatives are possible if Sanger sequencing is used alone without multiplex ligation-dependent probe amplification or next-generation sequencing.[40,41] The most frequently detected mutation was H1069Q, as described in all forms among Caucasians[41] and in the late-onset European cohort.[15] In France, all first-degree relatives of a patient with WD are screened for the disease, including family members above age 40 years. This allows the identification of about 20% of patients (French National Registry data).

Ten patients worsened in our study, mainly neurological patients and those on D-penicillamine, which is similar to what has been described in classic WD cohorts.[42] Zinc salt and trientine 2HCl were effective on neurological symptoms as first-line therapy with good tolerance, as in classic forms.[43,44] Liver disorders frequently worsened in screened patients (43%), in contrast to the other groups. Poor adherence to treatment in these asymptomatic patients may explain this deterioration.[45] In our cohort, 3 screened patients followed only a low-copper diet and did not worsen after 7 years of follow-up. Simple but regular follow-up visits could therefore be discussed in the exceptional cases of asymptomatic patients with normal copper levels, although an expert opinion is crucial in this decision. This is justified by the risk of treatment-induced copper deficiency, which can cause severe chronic sensorimotor polyneuropathy and myelopathy.[46,47] If the UCE and exchangeable copper values decrease below the normal threshold on therapy in association with leucopenia and anemia, physicians should consider lowering dosages or even discontinuing treatment with close monitoring.

Our study bears limitations. Its retrospective nature and the small number of patients limited our data analyses. However, the organization of the FWDR allowed us to obtain standardized and good-quality data. The rarity of WD itself does not allow for prospective studies with reasonably large sample sizes. In addition, three mutations in the patients with atypical neurological WD forms were novel; although in silico prediction tools suggested their pathogenic effect, gene expression studies are yet required to confirm their pathogenicity.

In conclusion, WD should be considered regardless of age, particularly because its presentation can be highly heterogeneous, with brain MRI abnormalities limited to atrophy and no KFR. Genetic testing confirms the diagnosis and should be performed in all first-degree members of a patient with WD. The prognosis of late-onset forms seems to be good when the treatment is personalized.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Poujois A, Woimant F. Wilson's disease: a 2017 update. Clin Res Hepatol Gastroenterol 2018;42:512–520. https://doi.org/10.1016/j.clinre.2018.03.007
2. European Association for the Study of the Liver. EASL clinical practice guidelines: Wilson's disease. J Hepatol 2012;56:671–685. https://doi.org/10.1016/j.jhep.2011.11.007
3. Poujois A, Girardot N, Brunet AS, Lachaux A, Woimant F. Contribution of the French registry in the understanding of Wilson disease. Mov Disord 2018;33:S217–S218.
4. Litwin T, Gromadzka G, Członkowska A. Gender differences in Wilson's disease. J Neurol Sci 2012;312:31–35. https://doi.org/10.1016/j.jns.2011.08.028
5. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. Gut 2007;56:115–120. https://doi.org/10.1136/gut.2005.087262
6. Ala A, Borjigin J, Rochwarger A, Schilsky M. Wilson disease in septuagenarian siblings: raising the bar for diagnosis. Hepatology 2005;41:668–670. https://doi.org/10.1002/hep.20601
7. Žigrai M, Vyskočil M, Tóthová A, Vereš P, Bluska P, Valkovič P. Late-Onset Wilson's Disease. Front Med 2020;7:26. https://doi.org/10.3389/fmed.2020.00026
8. Weitzman E. Late onset fulminant Wilson's disease: a case report and review of the literature. World J Gastroenterol 2014;20:17656. https://doi.org/10.3748/wjg.v20.i46.17656
9. Sukezaki A, Chu P, Shinoda M, et al. Late-onset acute liver failure due to Wilson's disease managed by plasmapheresis and hemodiafiltration successfully serving as a bridge for deceased donor liver transplantation: a case report and literature review. Clin J Gastroenterol 2020;13:1239–1246. https://doi.org/10.1007/s12328-020-01175-8
10. Shribman S, Webb G, Taylor R, et al. Liver transplantation for late-onset presentations of acute liver failure in Wilson's disease: the UK experience over 2 decades. JHEP Rep 2020;2:100096. https://doi.org/10.1016/j.jhepr.2020.100096

11. El Imad T, Al Moussawi H, Haddad FG, Felix R, Mulrooney SM. Wilson's disease: expect the unexpected. *Cureus* 2018;10:e2173. https://doi.org/10.7759/cureus.2173
12. Amano T, Matsubara T, Nishida T, et al. Clinically diagnosed late-onset fulminant Wilson's disease without cirrhosis: a case report. World J Gastroenterol 2018;24:290–296. https://doi.org/10.3748/wjg.v24.i2.290
13. Yousefi M, Yousefi M, Gharravi AM. Late-onset Wilson disease in older patient without ophthalmological findings, a case report. Clin Case Rep 2019;7:1253–1258. https://doi.org/10.1002/ccr3.2203
14. Dhakal B, Prabhat KC, Karki A, Bhattarai AM, Sapkota S, Subedi B, Dahal A. Late onset Wilson disease with normal neuropsychiatric status: a case report. Ann Med Surg 2022;77:103678. https://doi.org/10.1016/j.amsu.2022.103678
15. Ferenci P, Członkowska A, Merle U, et al. Late-onset Wilson's disease. Gastroenterology 2007;132:1294–1298. https://doi.org/10.1053/j.gastro.2007.02.057
16. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease[1]: diagnosis and phenotypic classification of Wilson disease. Liver Int 2003;23:139–142. https://doi.org/10.1034/j.1600-0676.2003.00824.x
17. Chevalier K, Mauget-Faÿsse M, Vasseur V, Azar G, Obadia MA, Poujois A. Eye involvement in Wilson's disease: a review of the literature. J Clin Med 2022;11:2528. https://doi.org/10.3390/jcm11092528
18. Poujois A, Trocello J-M, Djebrani-Oussedik N, et al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease. Eur J Neurol 2017;24:154–160. https://doi.org/10.1111/ene.13171
19. Twomey PJ, Viljoen A, Reynolds TM, Wierzbicki AS. Non-ceruloplasmin-bound copper in routine clinical practice in different laboratories. J Trace Elem Med Biol 2008;22:50–53. https://doi.org/10.1016/j.jtemb.2007.11.001
20. Woimant F, Djebrani-Oussedik N, Poujois A. New tools for Wilson's disease diagnosis: exchangeable copper fraction. Ann Transl Med 2019;7:S70. https://doi.org/10.21037/atm.2019.03.02
21. El Balkhi S, Trocello J-M, Poupon J, Chappuis P, Massicot F, Girardot-Tinant N, Woimant F. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis. Clin Chim Acta 2011;412:2254–2260. https://doi.org/10.1016/j.cca.2011.08.019
22. Trocello J-M, El Balkhi S, Woimant F, Girardot-Tinant N, Chappuis P, Lloyd C, Poupon J. Relative exchangeable copper: a promising tool for family screening in Wilson disease: RELATIVE EXCHANGEABLE COPPER: a WD TOOL. Mov Disord 2014;29:558–562. https://doi.org/10.1002/mds.25763
23. Guillaud O, Brunet A-S, Mallet I, et al. Relative exchangeable copper: a valuable tool for the diagnosis of Wilson disease. Liver Int 2018;38:350–357. https://doi.org/10.1111/liv.13520
24. Dusek P, Smolinski L, Redzia-Ogrodnik B, et al. Semiquantitative scale for assessing brain MRI abnormalities in Wilson disease: a validation study. Mov Disord 2020;35:994–1001. https://doi.org/10.1002/mds.28018
25. Gupta A, Lang AE. Psychogenic movement disorders. Curr Opin Neurol 2009;22:430–436. https://doi.org/10.1097/WCO.0b013e32832dc169
26. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424. https://doi.org/10.1038/gim.2015.30
27. Kim HJ, Yoon JH. A case of Wilson's disease presenting with paroxysmal dystonia. Neurol Sci 2017;38:1881–1882. https://doi.org/10.1007/s10072-017-3008-4
28. Tinazzi M, Geroin C, Erro R, et al. Functional motor disorders associated with other neurological diseases: beyond the boundaries of "organic" neurology. Eur J Neurol 2021;28:1752–1758. https://doi.org/10.1111/ene.14674
29. Wissel BD, Dwivedi AK, Merola A, et al. Functional neurological disorders in Parkinson disease. J Neurol Neurosurg Psychiatry 2018;89:566–571. https://doi.org/10.1136/jnnp-2017-317378
30. Ambar Akkaoui M, Geoffroy PA, Roze E, Degos B, Garcin B. Functional motor symptoms in Parkinson's disease and functional parkinsonism: a systematic review. J Neuropsychiatry Clin Neurosci 2020;32:4–13. https://doi.org/10.1176/appi.neuropsych.19030058
31. Espay AJ, Morgante F, Purzner J, Gunraj CA, Lang AE, Chen R. Cortical and spinal abnormalities in psychogenic dystonia. Ann Neurol 2006;59:825–834. https://doi.org/10.1002/ana.20837
32. Avanzino L, Martino D, van de Warrenburg BPC, et al. Cortical excitability is abnormal in patients with the "fixed dystonia" syndrome. Mov Disord 2008;23:646–652. https://doi.org/10.1002/mds.21801
33. Litwin T, Gromadzka G, Członkowska A, Gołębiowski M, Poniatowska R. The effect of gender on brain MRI pathology in Wilson's disease. Metab Brain Dis 2013;28:69–75. https://doi.org/10.1007/s11011-013-9378-2
34. Faa G, Lisci M, Caria MP, et al. Brain copper, iron, magnesium, zinc, calcium, sulfur and phosphorus storage in Wilson's disease. J Trace Elem Med Biol 2001;15:155–160. https://doi.org/10.1016/S0946-672X(01)80060-2
35. Kluska A, Kulecka M, Litwin T, et al. Whole-exome sequencing identifies novel pathogenic variants across the *ATP7B* gene and some modifiers of Wilson's disease phenotype. Liver Int 2019;39:177–186. https://doi.org/10.1111/liv.13967
36. Merico D, Spickett C, O'Hara M, et al. ATP7B variant c.1934T > G p.Met645Arg causes Wilson disease by promoting exon 6 skipping. NPJ Genomic Med 2020;5:16. https://doi.org/10.1038/s41525-020-0123-6
37. Poujois A, Woimant F. Challenges in the diagnosis of Wilson disease. Ann Transl Med 2019;7:S67. https://doi.org/10.21037/atm.2019.02.10
38. Steindl P, Ferenci P, Dienes H, et al. Wilson's disease in patients presenting with liver disease: a diagnostic challenge. Gastroenterology 1997;113:212–218. https://doi.org/10.1016/S0016-5085(97)70097-0
39. Walshe JM. The pattern of urinary copper excretion and its response to treatment in patients with Wilson's disease. QJM 2011;104:775–778. https://doi.org/10.1093/qjmed/hcr073
40. Coffey AJ, Durkie M, Hague S, et al. A genetic study of Wilson's disease in the United Kingdom. Brain 2013;136:1476–1487. https://doi.org/10.1093/brain/awt035
41. Chang IJ, Hahn SH. The genetics of Wilson disease. Handbook of Clinical Neurology. Amsterdam: Elsevier; 2017:19–34. https://doi.org/10.1016/B978-0-444-63625-6.00003-3.
42. Sohtaoglu M, Ergin H, Özekmekçi S, Gökdemir S, Sonsuz A, Arici C. Patient with late-onset Wilson's disease: deterioration with penicillamine. Mov Disord 2007;22:290–291. https://doi.org/10.1002/mds.21201
43. Woimant F, Debray D, Morvan E, Obadia MA, Poujois A. Efficacy and safety of two salts of trientine in the treatment of Wilson disease. J Clin Med 2022;11:3975. https://doi.org/10.3390/jcm11143975
44. Członkowska A, Litwin T, Karliński M, Dziezyc K, Chabik G, Czerska M. D-penicillamine versus zinc sulfate as first-line therapy for Wilson's disease. Eur J Neurol 2014;21:599–606. https://doi.org/10.1111/ene.12348
45. Jacquelet E, Poujois A, Pheulpin MC, Demain A, Tinant N, Gastellier N, Woimant F. Adherence to treatment, a challenge even in treatable metabolic rare diseases: a cross sectional study of Wilson's disease. J Inherit Metab Dis 2021;1481–1488. https://doi.org/10.1002/jimd.12430
46. Foubert-Samier A, Kazadi A, Rouanet M, Vital A, Lagueny A, Tison F, Meissner W. Axonal sensory motor neuropathy in copper-deficient Wilson's disease: neuropathy in WD. Muscle Nerve 2009;40:294–296. https://doi.org/10.1002/mus.21425
47. Lozano Herrero J, Muñoz Bertrán E, Ortega González I, Gómez Espín R, López Espín MI. Myelopathy secondary to copper deficiency as a complication of treatment of Wilson's disease. Gastroenterol Hepatol 2012;35:704–707. https://doi.org/10.1016/j.gastrohep.2012.03.008

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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